PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

DUE ON OCT 0 5 2005

PCT

To:
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Reply to:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	11 April 2005 (11-04-2005)
Applicant's or agent's file reference 15922-3PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/002070	02 December 2004 (02-12-2004)	05 December 2003 (05-12-2003)

International Patent Classification (IPC) or both national classification and IPC

IPC[7]: A61K-41/00, A61N-5/06, A61K-35/4, A61K-35/12,A61K-39/00, A61P-7/02

Applicant
UNIVERSITE DE MONTREAL ET AL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[ ]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.
[ ]	Box No. VI	Certain documents cited
[X]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA *Canadian Intellectual Property Office* *Place du Portage I, C114 - 1st Floor, Box PCT* *50 Victoria Street* *Gatineau, Quebec K1A 0C9* Facsimile No: 001(819)953-2476	Authorized officer Ryan Jaecques (819) 953-6570

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language which it was filed, unless otherwise indicated under this item.

   [ ] This opinion has been established on the basis of a translation from the original language into the following language _____ ,which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      [ ] a sequence listing

      [ ] table(s) related to the sequence listing

   b. format of material

      [ ] in written format

      [ ] in computer readable form

   c. time of filing/furnishing

      [ ] contained in the international application as filed.

      [ ] filed together with the international application in computer readable form.

      [ ] furnished subsequently to this Authority for the purposes of search.

3. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of :

[ ] the entire international application

[X] claim Nos. 1-12, 14-17, 32-43 and 45-48

because:

[X] the said international application, or the said claim Nos. 1-12, 14-17, 32-43 and 45-48 relate to the following subject matter which does not require an international preliminary examination *(specify)* :

The subject matter of claims 1-12, 14-17, 32-43 and 45-48 relates to a method of medical treatment of the human or animal body under Rule 39.1 (iv) PCT. For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exists in the PCT. The patentability can also be dependent upon the formulation of the claims. Certain national offices do accept claims worded as method of medical treatment while others rather accept claims worded as use claims and would then recognize the industrial applicability of these claims. Under the PCT Rules, no industrial applicability can be acknowledged. With regard to the above-cited claims, it should be noted that Rule 39.1 (iv) PCT is relevant insofar as independent claims 1 and 32 define a treatment of cells which may be effected *in vivo*.

[ ] the description, claims or drawings *(indicate particular elements below)* or said claim Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)* :

[ ] the claims, or said claim Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

[ ] no international search report has been established for said claim Nos. _____

[ ] the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that :

the written form [ ] has not been furnished

[ ] does not comply with the standard

the computer readable form [ ] has not been furnished

[ ] does not comply with the standard

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not

[ ] See Supplemental Box for further details.

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	8, 17, 28, 39 and 48	YES
	Claims	1-7, 9-16, 18-27, 29-38 and 40-47	NO
Inventive step (IS)	Claims		YES
	Claims	1-48	NO
Industrial applicability (IA)	Claims	13, 18-31 and 44	YES
	Claims		NO

2. Citations and explanations :

Reference is made to the following documents:

D1: WO 02/079183 A1 (HABI ET AL.)

D2: WO 01/24824 A1 (ROY ET AL.)

D3: WO 96/07431 A1 (GABOURY ET AL.)

D4: US 5 773 460 B (GABOURY ET AL.)

D5: GUIMOND, M ET AL. "P-Glycoprotein Targeting: A Unique Strategy to Selectively Eliminate Immunoreactive T Cells", *Blood*, 100(2) (15 July 2002), pp. 375-382

D6: CHEN, B. J. ET AL. "Prevention of Graft-versus-host Disease While Preserving Graft-versus-leukemia Effect After Selective Depletion of Host-reactive T Cells by Photodynamic Cell Purging Process", *Blood*, 99(9) (1 May 2002), pp. 3083-3088

D7: BRASSEUR, N. ET AL. "Eradication of Multiple Myeloma and Breast Cancer Cells by TH9402-Mediated Photodynamic Therapy: Implication for Clinical *Ex Vivo* Purging of Autologous Cell Transplants", *Photochem. Photobiol.*, 72(6) (2000), pp. 780-787

Summary of the Invention:

The present invention relates to the use of photodynamic therapy (PDT) in the treatment of immunologic disorders, infections and cancers. Central to the invention is the exposure of photoactivatable rhodamine derivatives to a sample of cells, which can later be reintroduced into the body. Cells that are activated tend to localize these compounds and result in the destruction of these cells once exposed to an activating (visible) light source, since the activated form of these compounds is very cytotoxic. The compounds are also known to have a low potential for DNA damage, mutation and/or carcinogenesis associated with their use. Cells that may be subject to this PDT include immune cells, infected cells and cancer cells. Destruction of the activated cells results in a release of antigen which is able to act as a vaccine upon reintroduction to the patient and initiates an immune response which, in turn, can effect the phrophylaxis and/or treatment of immunologic disorders, infection and cancers.

Summary of the Cited Art:

D1 discloses the production of rhodamine derivatives (including TH9402) that function as photosensitizers, and which preferentially localize in immunoreactive cells, where these cells can be subsequently destroyed by exposing them to visible light (PDT). The treatment may be in conjunction with an acceptable pharmaceutical carrier for the *ex vivo* elimination of reactive immune cells in patients with immunologic disorders. These rhodamines were found to be effective in preventing graft-versus-host disease (GVHD), and in the treatment of infections caused by Gram+ and/or Gram- bacteria, viral infections, leukemias, multiple myelomas and lymphomas, and solid tumours.

D2 discloses photoactivatable pharmaceutical compositions for the selective destruction of immunoreactive cells by using PDT in conjunction with a rhodamine derivative as photosensitizer (including TH9402). This was accomplished *ex vivo*, for the treatment of immunologic disorders, GVHD and organ rejection.

(Continued in Supplemental Box)

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted :

In the description, the reference cited on line 26-27 of page 2 (by McLaughlin et al.) contains a typographical error: the correct publication number is WO 97/37654.

The description does not comply with Article 5 PCT. While the application is written in English, page 16 (lines 4-5) contains text written in French. For clarity, an application should be submitted in only one of the PCT prescribed languages.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

The following claims do not comply with Article 6 PCT for the reasons given:

- In claims 1, 18 and 32, the term "supernatant" should be replaced by "lysate" for clarity (*cf.* page 14 line 13).
- In claims 1, 2, 32 and 33, the term "compound" is inappropriate in this context, since it is a generally-accepted synonym for a molecule, which these claims are not directed to. It is suggested that the term be replaced with "medicament" to avoid ambiguity.
- In claims 1, 22 and 32, the inclusion of "prevention" and "prophylaxis" (twice in claim 1) is ambiguous since they are synonymous terms, making it unclear what distinction is to be made between them.
- In claims 1, 22 and 32, it is unclear what is meant by "protection" (twice in claim 1). If it was intended to mean the same thing as "prevention" and "prophylaxis", then it should be removed for clarity. If there is an alternative definition intended by the applicant, this should be clarified.
- In claims 1 and 32, there is no antecedence for "individual cells".
- in claim 1, the claims refer to the manufacture of a type of medicament; however, the use of the medicament should not be defined as a causation (i.e. that it *causes* treatment or prophylaxis). It is preferable that the claims define the manufacture of a medicament, produced by the desired steps, for use in the treatment or prophylaxis of the diseases/conditions.
- In claims 12 and 43, reference to *in vitro* and *ex vivo* treatments is ambiguous since, typically, these two terms are considered synonymous in the art.
- In claims 13 and 44, the *ex vivo* treatment of the cells is defined as being via perfusion, however, the general definition of "perfusion" is the passage of fluid through a tissue or organ. It is thus unclear how this can be accomplished *ex vivo*, nor is any explanation provided in the description (*vide infra*).
- In claims 15, 16, 20, 21, 46 and 47, the language of these claims is unclear. Preferably, the claims should indicate that "said wavelength is in the range of. . . ."

The description does not comply with Article 5 PCT, as not being written in clear terms. Page 14 (lines 29-31) appears to explain how the *ex vivo* treatment of cells is performed via perfusion. However, the wording of this passage is unclear and thus does not serve to clarify how this is accomplished, nor does it serve to obviate objections to claims 13 and 44 under Article 6 PCT (*vide supra*).

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

D3 discloses the synthesis of photosensitive rhodamine derivatives that are useful in PDT. Also disclosed is the preferential localization of these compounds in malignant cells, and their use in the treatment of tumours and in bone marrow purging for autologous transplantation.

D4 discloses photoactivatable rhodamine derivatives, including some of those encompassed by the present claims, for use in PDT. These derivatives were found to be preferentially localized in malignant cells, which lead to the selective destruction of these cells and lead to the *in vitro* treatment of tumours via the purging of cancerous clones in the bone marrow of chronic myelogenous leukemia (CML) patients.

D5 discloses that PDT of TH9402-exposed T-cells led to the selective elimination of immunoreactive T-cell populations, and determined that this can be applied to in the treatment of GVHD and other alloimmune and autoimmune disorders.

D6 discloses that mice injected with irradiated allologous spleen cells previously treated with TH9402 and exposed to visible light at 514 nm (photodynamic cell purging or PDP) allowed 90% of the recipients to remain tumour-free and free of GVHD for a 100 day observation period, and yet graft-versus-leukemia (GVL) activity is not impaired.

D7 discloses the use of the photosensitizer TH9402 and visible light in the PDT-mediated selective elimination of CML and breast cancer cells.

Novelty and Inventive Step:

With regard to novelty, claims 1-7, 9-16, 18-27, 29-38 and 40-47 do not comply with Article 33(2) PCT as not being novel over one or more of **D1-D7**.

- Claims 1 and 2 relate to a medicament comprising PDT-treated cells wherein the cells are first treated with a defined rhodamine derivative, and then exposed to a light source to "activate" the compound. Each of **D1-D7** teaches the use of one or more of the rhodamine derivatives of the present claims for photodynamic therapy (PDT). Since, after treatment of the cells, they are readministered to the patient, this is seen as qualifying as use as a vaccine, and thus each is found prejudicial to the novelty of claims 1 and 2. The subject-matter of claim 32 is directed toward a method for preparing an immunologic medicament which, in substance, is that of claim 1, this claim is therefore also seen to lack novelty.

- Claims 3, 4, and 33-35 are directed to the use of the PDT-cell medicament in the treatment of alloimmune and/or autoimmune disorders (claims 3, 33 and 34) and GVHD and/or organ rejection (claims 4 and 35). However, each of **D1, D2, D5** and **D6** previously disclosed the use of this technique for these purposes.

- Claims 5 and 36 relate to a variety of immunologic disorders, some of which were previously disclosed in **D1** or **D2**.

- Claims 6, 7, 37 and 38 further define the infectious or viral source, both of which were disclosed in **D1**.

- Claims 9-11 and 40-42 more specifically define the cancer types which are treatable with the PDT-treated cells of the present invention, but **D1, D3, D4** and **D7** each previously disclosed PDT-therapy with identical rhodamine derivatives for use in the treatment of at least one of the cancers of these claims.

- Claims 12-16 and 43-47 further define where the cell treatment is performed (*in vivo* or *ex vivo*), the preferred rhodamine derivatives, and the wavelength of the activating light; however, this matter was previously disclosed in each of **D1-D7**.

- Claims 18-27 and 29-31 are essentially identical to the preceding claims, however, independent claim 18 (from which the others depend) defines an immunological vaccine comprising PDT-treated cells in combination with a pharmaceutical carrier. Such a vaccine was previously reported in **D1** alone.

With respect to the remaining claims: Claims 8, 28 and 39 are seen as novel over the prior art since none of these documents disclosed the treatment of diseases of parasitic origin. Similarly, claims 17 and 48 appear to be novel, since none of the prior art suggested the addition of antigen presenting cells to the medicaments previously defined. Therefore, claims 8, 17, 28, 39 and 48 comply with Article 33(2) PCT as being novel over the prior art.

(Continued in Supplemental Box 2)

Supplemental Box 2

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Supplemental Box

Regarding inventiveness: in view of the lack of novelty of claims 1-7, 9-16, 18-27, 29-38 and 40-47 under Article 33(2) PCT, these claims are also viewed as lacking inventive step under Article 33(3) PCT. Moreover, claims 8, 17, 18-25, 28-31, 39 and 48 also do not comply with Article 33(3) PCT as defining subject-matter that would have been obvious to a person skilled in the art in light of the disclosures of **D1-D4**. Claims 8, 28 and 39 are essentially identical in that each of these claims specifies that the previously defined infection results in Chagas' disease. This disease is known to be a result of contact with the parasite *Trypanosoma cruzi*, which may have an intracellular component. Since this would effectively "activate" the cells similar to other infectious agents, it would have been obvious to a person skilled in the art (in light of **D1**, for instance) to apply this medicament of these claims for this purpose. Claims 17 and 48 are directed toward the addition of antigen presenting cells to the previously defined medicament. However, since antigen presenting cells are commonly known to help initiate immune response of T cells, it would be obvious to combine these cells with the PDT-treated cells, such that they would be in close proximity with the released antigens, and it would be expected that the immune response would be facilitated. Claims 18-22 are seen as lacking inventive step over **D2-D4**, in that these claims are essentially identical to the subject-matter of claims 1, 14 and 15, except that they pertain to an identical medicament as defined by claim 1 in combination with a pharmaceutically acceptable carrier. Addition of such a carrier is well known in the art, and it is well within the skill-set of an ordinary worker to add one if deemed desirable. Claims 23-25, in light of **D2**, and claims 29-31, in light of **D3** and **D4**, are thus also deemed to lack inventive ingenuity. Therefore, claims 8, 17, 18-25, 28-31, 39 and 48 do not comply with Article 33(3) PCT as not being inventive over one or more of **D1-D4**.

Industrial Applicability:

Claims 13, 18, and 44 are considered to comply with Article 33(4) PCT. Since immunologic disorders, infections and cancers are major causes of illness in society, a means by which these conditions may be treated using photodynamic therapy (PDT) with rhodamine derivatives is viewed as being of use in the medical field, and thus constitutes industrially applicable subject-matter.